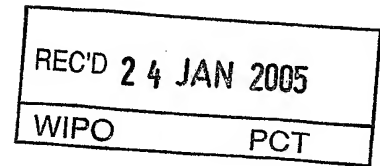


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The application was originally filed in English.

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Applicant (s)

(21) Patentansökningsnummer 0400014-7
Patent application number

(86) Ingivningsdatum 2004-01-08
Date of filing

Stockholm, 2004-11-11

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund
Hjördis Segerlund

Avgift
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HETEROCYCLIC DERIVATIVES

The invention relates to heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.

The antithrombotic and anticoagulant effect produced by the compounds of the invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by B.-Y. Zhu, R. M. Scarborough, Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs, 1999, 1(1), 63-88. Thus it is known that two proteins, one known as recombinant antistasin (r-ATS) and the other known as recombinant tick anticoagulant protein (r-TAP), are specific direct Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by B.-Y. Zhu and R. M. Scarborough, many inhibitors possess a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that certain heterocyclic derivatives possess Factor Xa inhibitory activity. Many of the compounds of the present invention also possess the advantage of being selective Factor Xa inhibitors, that is the enzyme Factor Xa is inhibited strongly at concentrations of test compound which do not inhibit or which inhibit to a lesser extent the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

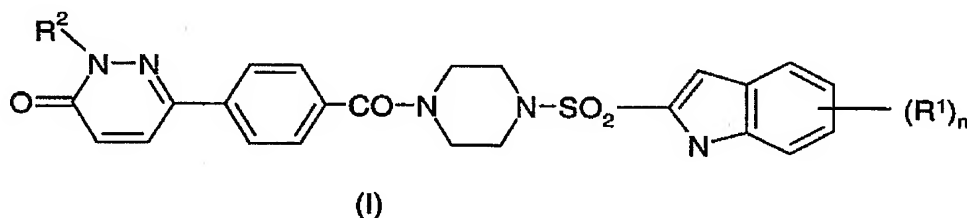
The compounds of the present invention possess activity in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated,

for example in the treatment or prevention of thrombotic conditions such as coronary artery and cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the rupture of atherosclerotic plaques, venous or arterial thrombosis, 5 coagulation syndromes, vascular injury including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary 10 embolism, ischemia and angina (including unstable angina).

The compounds of the invention are also useful as inhibitors of blood coagulation in an *ex-vivo* situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

15 WO 98/21188 describes a range of Factor Xa inhibitors. Further particular examples of this type of compound including 1-(5-chloroindol-2-ylsulphonyl)-4-[4-(6-oxo-1H-pyridazin-3-yl) benzoyl]piperazine are described in WO 99/57113. The applicants have found however, that by further derivatising the compounds of this type, enhanced properties may be obtained.

20 The present invention provides a compound of formula (I)



wherein R^2 is amino, a group OR^4 or a group $-Y-R^5$ where R^4 is hydrogen or C_{1-4} alkyl,

25 Y is C_{1-4} alkylene,

R^5 is hydrogen, halo, hydroxy, C_{1-2} alkoxy, C_{1-2} alkoxy C_{1-2} alkoxy, or a group NR^7R^8

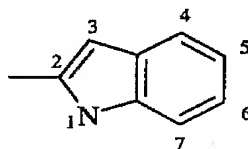
where R^7 and R^8 are independently selected from hydrogen, C_{1-2} alkyl, hydroxy C_{1-2} alkyl

or alkoxyC₁₋₂alkyl, or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a saturated 5-6-membered heterocyclic ring which optionally contains an additional heteroatom;

n is one or two and each R¹ is independently selected from halo, haloC₁₋₂alkyl, hydroxy, 5 oxo, amino, C₁₋₂alkylamino or di-C₁₋₂dialkylamino; and pharmaceutically acceptable salts thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

10 For the avoidance of doubt, the atoms of the indolyl ring appearing in formula (I) is numbered as drawn below:



2-indolyl

It is to be understood that certain heterocyclic derivatives of the present 15 invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Factor Xa inhibitory activity.

It is further to be understood that, insofar as certain of the compounds of the formula defined above may exist in optically active or racemic forms by virtue of one or 20 more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which possesses Factor Xa inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

25 Compounds of the invention are potent inhibitors of Factor Xa, and may have better solubility and/or less cytochrome P 450 (CYP₄₅₀) inhibition and/or Caco2-permeability than some related compounds. Caco2 is a cell line which mimics transport over the gut wall.

Suitable values R¹ and/or R² are:

- | | |
|---|--|
| <p>for C₁₋₄alkyl:</p> <p>for halo:</p> <p>for C₁₋₄alkylamino:</p> <p>5 for di-C₁₋₄alkylamino:</p> <p>for haloC₁₋₄alkyl:</p> <p>for aminoC₁₋₄alkyl</p> <p>10 for C₁₋₂alkylaminoC₁₋₄alkyl</p> <p>for di-C₁₋₂dialkylaminoC₁₋₄alkyl;</p> <p>15</p> <p>for hydroxyC₁₋₄alkyl:</p> <p>for C₁₋₂alkoxyC₁₋₄alkyl:</p> <p>20</p> <p>for C₁₋₄alkoxy:</p> | <p>methyl, ethyl, propyl, isopropyl and n-butyl, isobutyl;</p> <p>fluoro, chloro, bromo;</p> <p>methylamino, ethylamino, propylamino; dimethylamino, diethylamino, N-methyl-N-ethylamino;</p> <p>fluoromethyl, 1-fluoroethyl, 2-fluoroethyl, trifluoromethyl or trifluoroethyl.</p> <p>aminomethyl, or aminoethyl,</p> <p>methylaminomethyl, ethylaminomethyl, ethylaminoethyl, methylaminoethyl, dimethylaminomethyl, diethylaminomethyl, diethylaminoethyl, methylethylaminomethyl, methylethylaminoethyl.</p> <p>hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl;</p> <p>methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;</p> <p>methoxy, ethoxy;</p> |
|---|--|

In particular, R² is a group -Y-R⁵.

Suitably Y is a C₁₋₂alkylene group.

- 25 Examples of groups R⁵ are hydrogen, halo, hydroxy, methoxy, methoxyC₁₋₂alkoxy, or a group NR⁷R⁸ where R⁷ and R⁸ are as defined above.

A preferred group R⁵ is hydrogen, so that particular examples of R² are methyl or ethyl. A particularly preferred example of R² is methyl.

- In an alternative embodiment, R² is a group -Y-R⁵ where R⁵ a group NR⁷R⁸
- 30 where R⁷ and R⁸ are independently selected from hydrogen, C₁₋₂alkyl, hydroxyC₁₋₂alkyl or alkoxyC₁₋₂alkyl, or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a saturated 5-6-membered heterocyclic ring which optionally contains an

additional heteroatoms. Suitably at least one of R^7 or R^8 is a hydroxy C_{1-2} alkyl or alkoxy C_{1-2} alkyl group, such as methoxyethyl.

In particular, where R^7 and R^8 together form a saturated heterocyclic ring, it contains a further heteroatom selected from oxygen and sulphur, and in particular oxygen. Particular examples of such groups are morpholino.

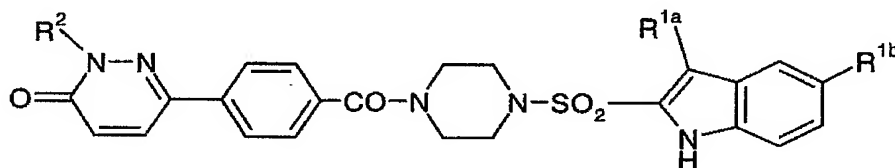
Preferably n is 1 or 2, and most preferably, it is 1.

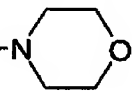
Particular groups R^1 are halo groups such as bromo or chloro. Preferably a group R^1 is present at a position equivalent to the 5-position as numbered on the indole ring.

Particular compounds of the invention are shown in the following Table.

10

Table

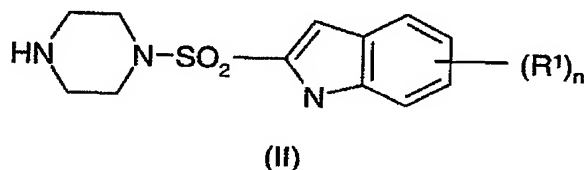


Compound No.	R^2	R^{1a}	R^{1b}
1	CH ₃	H	Cl
2	-(CH ₂) ₂ N(CH ₃) ₂	H	Cl
3	-(CH ₂) ₂ NH(CH ₃)	H	Cl
4	-CH ₃	F	Cl
5	-CH ₂ CH ₃	H	Cl
6	-(CH ₂) ₃ CH ₃	H	Cl
7	-(CH ₂) ₂ OH	H	Cl
8	-CH ₂ CF ₃	H	Cl
9	-(CH ₂) ₂ OCH ₃	H	Cl
10	-(CH ₂) ₂ O(CH ₂) ₂ OCH ₃	H	Cl
11	—(CH ₂) ₂ —N— 	H	Cl
12	-(CH ₂) ₂ NH(CH ₂) ₂ OCH ₃	H	Cl

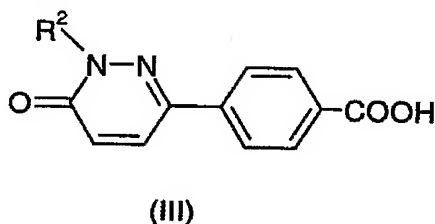
A heterocyclic derivative of formula I, or pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of related compounds, such as those described in WO 98/21188 and WO 99/57113. Such
 5 procedures are provided as a further feature of the invention and are illustrated by the following representative processes in which, unless otherwise stated any functional group, for example amino, aminoalkyl, carboxy, indolyl or hydroxy, is optionally protected by a protecting group which may be removed when necessary.

Necessary starting materials may be obtained by standard procedures of
 10 organic chemistry and by reference to the processes used in the Examples.

For instance, the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises the reaction, conveniently in the presence of a suitable base, of an amine of formula (II)



15 with an acid of the formula (III)



wherein R^2 is as defined above in relation to formula (I), or a reactive derivative thereof.

A suitable reactive derivative of an acid of the formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an
 20 inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated amide such as 1,1'-carbonyldiimidazole; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol

such as N-hydroxybenzotriazole or N-hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid
5 and a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide.

The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, and at
10 a temperature in the range, for example, -78 °C to 150 °C, conveniently at or near ambient temperature.

A suitable protecting group for an amino or aminoalkyl group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-
15 butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis
20 with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric, phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation
25 over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

30 A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group.

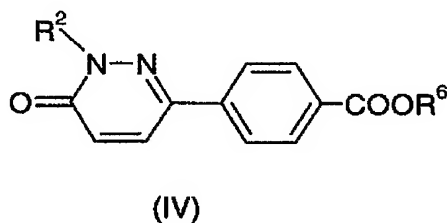
Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. An arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as

5 palladium-on-carbon.

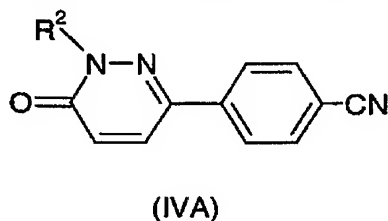
A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for

10 example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Compounds of formula (III) are suitably prepared by deprotecting a compound of formula (IV)

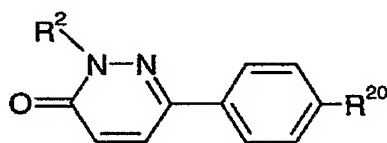


15 where R⁶ is an acid protecting group such as a C₁₋₆alkyl group, and in particular methyl or ethyl. This may be removed using methods described above for the removal of esterifying protecting groups. Alternatively, compounds of formula (III) can be prepared by hydrolysis of a compound of formula (IVA)



Generally, this reaction is carried out by reacting the compound of formula (IVA) with an acid such as a strong mineral acid, for instance, sulphuric acid, at elevated temperatures, for example from 50 °C to 150°C, and subsequent reaction with a base such as sodium hydroxide, to form the corresponding benzamide. This can then be dissolved in an organic solvent such as an alcohol, such as ethanol, and treated with sodium hydroxide to produce the desired acid. Alternatively the nitrile group is hydrolysed by alkali metal hydroxides in aqueous solutions at temperatures of from 20°C to 150 °C.

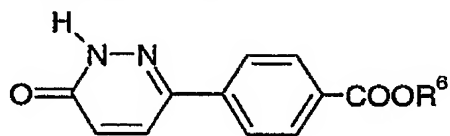
Compounds of formula (IVA) can be prepared from compounds of formula (IVB)



(IVB)

where R^{20} is a halo group by conventional methods. For instance using CuCN in dimethylformamide or 1-methyl-2-pyrrolidinone or by palladium catalysis using e.g. $Pd(PPh_3)_4$ and $Zn(CN)_2$ in DMF or $Pd(OAc)_2$, PPh_3 and $Zn(CN)_2$ in 1-methyl-2-pyrrolidinone at temperatures of from 0 °C to 150 °C.

In an alternative embodiment, the compound of formula (IV) is obtained by alkylation of a compound of formula (IVC)



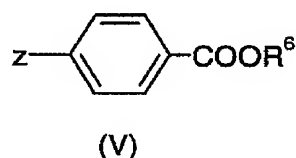
(IVC)

where R^6 is as defined above, with a compound of formula (A)



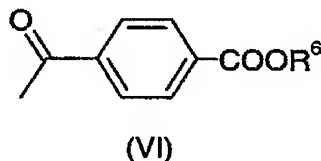
where R^2 is as defined in relation to formula (I) and Z''' is a displaceable group such as halogen or sulphonate. The reaction suitably is carried out in an organic solvent such as dimethylformamide, 1,4-dioxane, dimethylsulphoxide, 1-methyl-2-pyrrolidinone, tetrahydrofuran, toluene or dichloromethane at temperatures in the range of from -78°C to 150°C in the presence of a base such as an alkali or alkaline earth metal carbonate.

Compounds of formula (IV) can be prepared by forming a pyridazinone ring on a compound of formula (V),

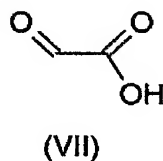


wherein Z is a functional group capable of cyclisation, using methods which are known in the literature.

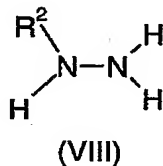
For example, compounds of formula (IV) may be prepared by reacting a compound of formula (VI)



wherein R^6 is as defined in relation to formula (IV), with a compound of formula (VII)



and subsequently reacting the intermediate produced with a compound of formula (VIII)



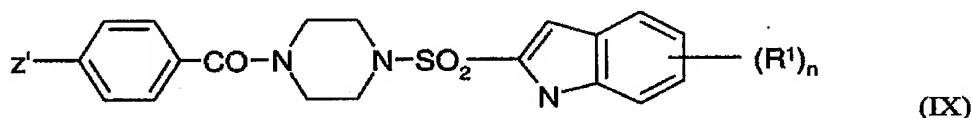
where R^2 is as defined in relation to formula (I).

The reaction of compounds of formula (VI) with (VII) can be carried out directly in the absence of solvent or in the presence of a solvent such as acetic acid, tetrahydrofuran, 1,4-dioxane, ethanol, or methanol. Suitably it is effected in the presence of a base such as an alkali metal carbonate or an alkali metal hydroxide, for example potassium carbonate or potassium hydroxide. Temperatures in the range of from -20°C to 200°C may be employed, and any heating may be conveniently carried out using microwave heating.

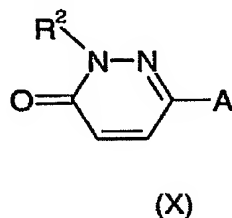
For the subsequent reaction of the product with the compound of formula (VIII), suitable reaction conditions include the optional use of an organic solvent such as dimethylsulphoxide, 1,4-dioxane, tetrahydrofuran, acetonitrile or water. Temperatures in the range from 0°C to 200°C can be used, and conveniently, the reaction is effected at the reflux temperature of the solvent.

Compounds of formula (VIII) are known compounds or can be prepared from known compounds using conventional methods.

Alternatively, a compound of formula (I) may be prepared by reaction of a compound of the formula (IX):



wherein Z' is a displaceable group such as halo, with a compound of formula (X)

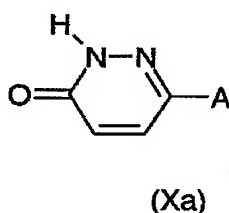


wherein R^2 is as defined in relation to formula (I) and A is an activating group. Suitable activating groups A include metalised derivatives, such as with zinc or tin, and borane derivatives. The compound of formula (X) is reacted with a compound of the formula (IX) to effect cross coupling where Z is triflate or a halo group, such as iodo, bromo or

chloro. Suitably the reaction is catalysed by use of a transition state metal catalyst, such as palladium, for example $\text{Pd}(\text{PPh}_3)_4$.

Alternatively it is possible that the compound of formula (X) contains the displaceable group Z and the phenyl ring is activated with the group A, and the reaction
5 performed as described above.

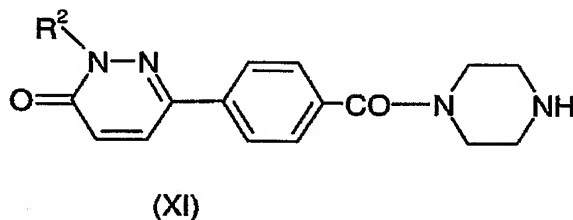
Compounds of formula (X) are either known compounds or they can be prepared by conventional methods, for example, by alkylation of compounds of formula compounds of formula (Xa)



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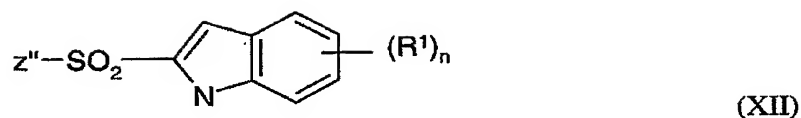
In yet another alternative, compounds of formula (I) can be prepared by forming an appropriately substituted pyridazinone ring on compounds of formula (IX), wherein Z' is a functional group capable of cyclisation. Suitable reagents and conditions
15 are described above in relation to the reaction between compounds (VI), (VII) and (VIII).

Compounds of formula (I) may also be prepared by reacting a compound of the formula (XI):



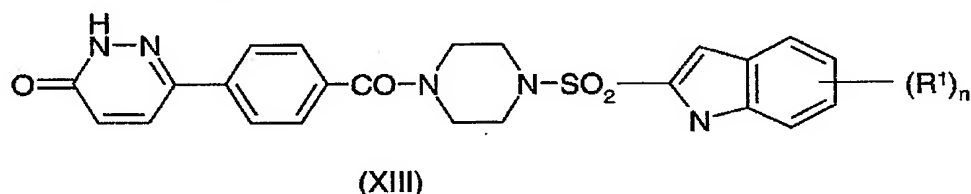
20

where R^2 is as defined in relation to formula (I), with a compound of the formula (XII):



wherein Z'' is a displaceable group for example chloro, under conditions similar to those described above for the reaction between compounds of formula (II) and (III).

- 5 In addition, compounds of formula (I) may be prepared by reacting a compound of formula (XIII)



- wherein R¹ and n are as defined in relation to formula (I), and the indole ring is optionally protected, with a compound of formula (A) as defined above, and thereafter
 10 if necessary, removing any indole protecting groups. Again reaction conditions are similar to those described above in relation to the reaction of the compound of formula (A) with a compound of formula (IVC).

Compounds of formula (XIII) can be prepared by methods described in see WO 99/57113. In particular, these methods are analogous to those described above, for the
 15 reaction of compound (II) with a compound of formula (III), but in this case the compound of formula (III) will be 4-(3-1H-pyrazin-6-onyl)-benzoic acid, which can be prepared by the method described by: Coates, W. J.; McKillop, A., *Synthesis*, **1993**, 334-342.

- When a pharmaceutically-acceptable salt of a compound of the formula (I) is
 20 required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure.

- When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said
 25 compound using a conventional procedure, for example by the formation of diastereomeric salts, use of chromatographic techniques, conversion using

stereospecific enzymatic processes, or by addition of temporary extra chiral group to aid separation.

As stated previously, the compounds of the formula (I) are inhibitors of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or
5 more of the standard procedures set out hereinafter:-

a) Measurement of Factor Xa Inhibition

The FXa inhibitor potency was measured with a chromogenic substrate method, in a Plato 3300 robotic microplate processor (Rosys AG, CH-8634 Hombrechtikon,
10 Switzerland), using 96-well, half-volume microtiter plates (Costar, Cambridge, MA, USA; Cat No 3690). Stock solutions of test substance in DMSO (72 μ L), 10 mmol/L, alternatively 1 mmol/L were diluted serially 1:3 (24 + 48 μ L) with DMSO to obtain ten different concentrations, which were analyzed as samples in the assay, together with controls and blanks. As control sample melagatran was analysed. The dilutions of each
15 test substance were analyzed consecutively, row-wise on the microtiter plate, with wash-cycles between substances to avoid cross-contamination. First 2 μ L of test sample or DMSO for the blank were added, followed by 124 μ L of assay buffer (0.05 mol/L Tris-HCl pH 7.4 at 37°C, 5 mM CaCl₂, ionic strength 0.15 adjusted with NaCl, 0.1 % bovine serum albumin, ICN Biomedicals, Inc, USA, 1g/L) and 12 μ L of chromogenic
20 substrate solution (S-2765, Chromogenix, Mölndal, Sweden) and finally 12 μ L of FXa solution (human FXa, Haematologic Technologies Inc., Essec Junction, Vermont, USA), in buffer, was added, and the samples were mixed. The final assay concentrations were: test substance 0.0068-133, respectively 0.00068-13.3 μ mol/L, S-2765 0.40 mmol/L (K_M = 0.25 mmol/L) and FXa 0.1 nmol/L. The linear absorbance
25 increase at 405 nm during 40 min incubation at 37 °C was used for calculation of percent inhibition for the test samples, as compared to references without inhibitor and/or enzyme. The IC₅₀-value, corresponding to the inhibitor concentration, which caused 50 % inhibition of the FXa activity, was calculated by fitting the data to a three-parameter equation by Microsoft XLfit.

30 b) Measurement of Thrombin Inhibition

The thrombin inhibitor potency was measured with a chromogenic substrate method developed in-house in principle as described in a) for FXa but using instead 0.3 mM of the chromogenic substrate solution S-2366 (Chromogenix, Mölndal, Sweden) and 0.1

nmol/L human thrombin (Haematologic Technologies Inc., Essec Junction, Vermont, USA).

c) Measurement of Anticoagulant Activity

An in vitro assay whereby human blood is collected and added directly to a sodium citrate solution (3.2 g/100 mL, 9 parts blood to 1 part citrate solution). Plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at -80°C .) and an aliquot was rapidly thawed at 37°C on the day of the experiment and kept on ice before addition to the coagulometer cups. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to double the clotting time is determined. Thromborel @ S (Dade Behring, Liederbach, Germany) was reconstituted with 10 mL water. This solution was kept at 4°C and was used within one week. Before the experiment the solution was kept at 37°C for at least 30 minutes before start of the experiment. A ball coagulation timer KC 10A from Heinrich Amelung GmbH. (Lemgo, Germany) was used to study if the compounds could prevent coagulation in human plasma. The time for 50 μL plasma with compound to coagulate after addition of 100 μL Thromborel S, the Prothrombin Time or PT_i , is compared with the time it takes for pure plasma to coagulate, PT_0 . With this technique the change in viscosity in the stirred solution is used to define clotting. The IC_{50} is calculated from the curve of PT_i/PT_0 versus the inhibitor concentration in plasma, *id est* three times the final assay concentration.

d) An in vivo Measurement of Antithrombotic Activity

The abdomen is opened and the caval vein exposed. The thrombotic stimulus is partial stasis to the caval vein and a piece of filter paper soaked with ferric chloride and superimposed to the external surface of the vein. Thrombus size is determined as the thrombus wet weight at the end of the experiment. (Ref Thromb. Res. 2002;107:163-168).

A feature of the invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a heterocyclic derivative of formula (I), or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a heterocyclic derivative of the formula (I), or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided a heterocyclic derivative of formula (I), or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes the use of such an active ingredient in the production of a medicament for use in:-

- (i) producing a Factor Xa inhibitory effect;
- (ii) producing an anticoagulant effect;
- (iii) producing an antithrombotic effect;
- (iv) treating a Factor Xa mediated disease or medical condition;
- (v) treating a thrombosis mediated disease or medical condition;
- (vi) treating coagulation disorders; and/or
- (vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of an active ingredient as defined hereinbefore.

5 The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the formula (I) are useful in the treatment or prevention of a
10 variety of medical disorders where anticoagulant therapy is indicated. In using a compound of the formula (I) for such a purpose, it will generally be administered so that a daily oral dose in the range, for example, 0.5 to 100 mg/kg body weight/day is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed, for example a dose for intravenous
15 administration in the range, for example, 0.01 to 10 mg/kg body weight/day will generally be used. For preferred and especially preferred compounds of the invention, in general, lower doses will be employed, for example a daily dose in the range, for example, 0.1 to 10 mg/kg body weight/day. In general a preferred dose range for either oral or parenteral administration would be 0.01 to 10 mg/kg body weight/day.

20 Although the compounds of formula (I) are primarily of value as therapeutic or prophylactic agents for use in warm-blooded animals including man, they are also useful whenever it is required to produce an anticoagulant effect, for example during the ex-vivo storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

25 The compounds of the invention may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a
30 thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

The invention will now be illustrated in the following Examples in which, unless otherwise stated:-

(i) Yields are given for illustration only and are not necessarily the maximum attainable;

(ii) The end-products have satisfactory high resolution mass spectral (HRMS) data as analysed on a Micromass LCT system equipped with a TOF mass spectrometer. MS conditions: Electrospray ionization, positive mode, capillary voltage 2.3 kV and desolvation temperature 150 °C. Accurate mass was determined for positive ionization using leucine enkephaline (m/z 556.2771) as lock mass. Structure were confirmed by nuclear magnetic resonance (NMR). Chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet;

(iii) Intermediates were generally characterised as the end products with the exception of HRMS data.

(ii). Purity was assessed by, high performance liquid chromatography instruments equipped with UV detectors operating at 254 nm and by NMR.

(iv) Purification of intermediates and products were done by flash chromatography or high performance reversed phase preparative liquid chromatography (HPLC).

Example 1

20 6-[4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl]-2-methyl-2H-pyridazin-3-one

Step A

4-Acetylbenzoic acid (5.00 gram, 30.5 mmol) and 3.19 gram of glyoxalic acid monohydrate (34.7 mmol, 1.14 eq.) were stirred in 50 mL of acetic acid at 110 °C for 20 hours, and then cooled to 40 °C. Solvent was removed with evaporator *in vacuo*. To the residue was added water (15 mL), and the mixture cooled with an ice bath. The resulting solution was titrated with ammonia solution until pH 9. Methyl hydrazine (3.00 mL 57.3 mmol, 1.88 eq.) was added, and the mixture was heated to reflux for 5 hours. The solution was concentrated *in vacuo*. To the solid residue was added 1 M cold aqueous hydrochloric acid until the solution had a pH 1 ~ 2. The solid was filtrated and dried *in vacuo* over night. The solids were treated with diethyl ether (200 mL) and the mixture was ultrasonicated at room temperature for 3 hours and filtered. The solids

were treated with 200 mL of diethyl ether and stirred for 2 hours before filtration, which after drying gave 4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid in 33 % isolated yield.

¹H NMR (300 MHz; *N,N*-dimethylformamide-*d*₇ as solvent and internal
5 reference) δ (ppm) 3.81 (s, 3H), 7.06 (d, 1H, *J* = 9.7 Hz), 8.04 - 8.16 (m, 5H).

Step B

To a solution of 4-(1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid, (0.637g, 2.76 mmol) in *N,N*-dimethylformamide was added 1,1'-carbonyldiimidazole
10 (0.930g, 5.74 mmol, 2.07 eq.). The resulting solution was stirred at room temperature for 5 hours, whereupon 5-chloro-2-(piperazin-1-ylsulphonyl)-1H-indole (see WO 99/57113, 0.622g, 2.08 mmol, 1.11eq.) was added. The reaction mixture was stirred at 25 °C for 14 h and then evaporated *in vacuo*. The residue was purified by flash column chromatography: first eluting with ethyl acetate : toluene (2 : 1), then with ethyl acetate.
15 During concentration of the desired fraction, a white solid precipitated. The solid was triturated with hot ethyl acetate (50 mL) to remove a trace of impurity. After drying, pale yellow solid were isolated. De-colorization on charcoal using hot methanol together with the re-crystallization in methanol, gave 0.79 gram 6-{4-[4-(5-chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one as
20 fine white crystals (yield 56 %).

¹H NMR (500 MHz; *N,N*-dimethylformamide-*d*₇ as solvent and internal
reference) δ (ppm) 3.23 (m, 4H), 3.50 - 3.90 (m, 4H), 3.78 (s, 3H), 7.03 (d, 1H, *J* = 9.6 Hz), 7.10 (m, 1H), 7.36 - 7.38 (m, 1H), 7.52 (m, 2H), 7.59 (m, 1H), 7.83 (m, 1H), 7.95 (m, 2H), 8.10 (d, 1H, *J* = 9.6 Hz).

25 HRMS (ESI+) calc. [M+H]⁺ 510.1003, found 510.1025.

Example 2

6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-dimethylamino-ethyl)-2H-pyridazin-3-one

Step A

To a microwave vial was added 3,6-dichloropyridazine (645mg, 4.33mmol), potassium acetate (425 mg, 4.33 mmol) and 9 mL acetic acid/water (5:1). The reaction mixture was heated at 140 °C for 70 minutes. The solvent was evaporated and the crude

was purified by preparative HPLC using a gradient of acetonitrile/ 5 % acetonitrile - water phase containing 0.1 M ammonium acetate, to give 436 mg of 6-chloro-2H-pyridazin-3-one (77 % yield).

¹H NMR (400 MHz; methanol-d₄ as solvent and internal reference) δ(ppm) 6.96 (d, 1H), 7.45 (d, 1H).

Step B

To a solution of 6-chloro-2H-pyridazin-3-one (500 mg, 3.83 mmol) in 5 mL dimethylformamide was added 2-dimethylaminoethyl chloride hydrochloride (828 mg, 5.75 mmol), potassium carbonate (1.59 g, 11.5 mmol) and sodium iodide (632 mg, 4.21 mmol). The mixture was stirred over night at 65 °C. Solvent was evaporated. The crude product was dissolved in water and purified by preparative HPLC using a gradient of acetonitrile/ 5 % acetonitrile - water phase containing 0.1 M ammonium acetate, to give 174 mg of 6-chloro-2-(2-dimethylamino-ethyl)-2H-pyridazin-3-one as light brown crystals after freeze drying (22 % yield).

¹H NMR (400 MHz; methanol-d₄ as solvent and internal reference) δ(ppm) 2.35 (s, 6H), 2.82 (t, 2H), 4.26 (t, 2H), 6.98 (d, 1H), 7.43 (d, 1H).

Step C

5-Chloro-2-(piperazin-1-ylsulphonyl)-1H-indole (5.42 g, 18.1 mmol) was added to a solution of 4-carboxyphenyl boronic acid (3.00 g, 18.1 mmol) *N,N*-diisopropylethylamine (2.34 g, 18.1 mmol) and O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (5.81 g, 18.1 mmol) in 80 mL *N,N*-dimethylformamide, the mixture was stirred for 2 hours at room temperature. *N,N*-Dimethylformamide was removed *in vacuo* and the crude was purified by flash chromatography three times (dichloromethane/methanol, 100 - 98/2) to give 4-({4-[(5-chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)phenyl boronic acid as a colourless solid (56 % yield).

¹H NMR (400 MHz; methanol-d₄ as solvent and internal reference) δ(ppm) 3.04 - 3.24 (m, 4H), 3.46 - 3.92 (m, 4H), 6.99 - 7.00 (m, 1H), 7.27 - 7.32 (m, 3H), 7.45 (d, 1H), 7.61 - 7.65 (m, 2H), 7.68 - 7.70 (m, 1H).

Step D

6-Chloro-2-(2-dimethylamino-ethyl)-2H-pyridazin-3-one (76 mg, 0.38 mmol), cesium carbonate (122 mg, 0.38 mmol) and bis(triphenylphosphine)palladium II chloride (21.9 mg, 0.03 mmol) was added to a microwave vial. The vial was evacuated and filled with argon twice. 4-({4-[(5-Chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)phenyl boronic acid (140 mg, 0.31 mmol) dissolved in 4 mL 1,2-dimethoxyethane/water/ethanol (7 : 3 : 2) was added and the vial was once again evacuated and filled with argon. The reaction mixture was heated at 150 °C for 100 seconds, filtrated and purified by preparative HPLC using a gradient of acetonitrile/ 5 % acetonitrile-water phase containing 0.1M ammonium acetate, to give 107mg of 6-{4-[4-(5-chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-dimethylamino-ethyl)-2H-pyridazin-3-one after evaporation and freeze drying over night (60 % yield).

¹H NMR (400 MHz; methanol-d₄ as solvent and internal reference) δ(ppm) 2.40 (s, 6H), 2.94 (t, 2H), 3.08 - 3.24 (m, 4H), 3.48 - 3.91 (m, 4H), 4.42 (t, 2H), 7.00 - 7.01 (m, 1H), 7.07 (d, 1H), 7.27 - 7.31 (m, 1H), 7.43 - 7.48 (m, 3H), 7.69 - 7.70 (m, 1H), 7.93 - 8.01 (m, 3H).

HRMS (ESI+) calc. [M+H]⁺ 569.1738, found 569.1758.

Example 3

6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-methylamino-ethyl)-2H-pyridazin-3-one

The compound was prepared according to the procedure for Example 2 in 26 % isolated yield from 4-({4-[(5-chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)-phenyl boronic acid.

¹H NMR (400 MHz; methanol-d₄ as solvent and internal reference) δ (ppm) 2.72 (s, 3H), 3.05 - 3.26 (m, 4H), 3.49 (t, 2H), 3.53 - 3.95 (m, 4H), 4.56 (t, 2H), 7.00 - 7.01 (m, 1H), 7.13 (d, 1H), 7.28 - 7.31 (m, 1H), 7.44 - 7.49 (m, 3H), 7.68 - 7.71 (m, 1H), 7.96 (d, 2H), 8.06 (d, 1H).

HRMS (ESI+) calc. [M+H]⁺ 555.1581, found 555.1559.

Example 4

6-[4-[4-(5-Chloro-3-fluoro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl]-2-methyl-2H-pyridazin-3-one

Step A

5 To 5-chloroisatin (5.00 g, 27.5 mmol), suspended in dry dichloromethane (250 mL) was added (diethylamino)sulphur trifluoride (7.64 mL, 57.8 mmol) and the mixture was stirred at room temperature for 48 h methanol (30 mL), was added, and the mixture was washed with water. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried (Na₂SO₄) and concentrated. Flash column
10 chromatography on silica gel (dichloromethane/diethyl ether 20:1) of the residue gave 3.55g (63 %) of 5-chloro-3,3-difluoro-1,3-dihydro-2H-indol-2-one.

¹H NMR (400 MHz, CDCl₃ as solvent and internal reference) δ 6.89 (dt, 1H, *J* = 1.5, 8.4 Hz), 7.42 - 7.45 (m, 1H), 7.54 (q, 1H, *J* = 1.8 Hz), 7.99 (broad s, 1H).

15 **Step B**

To a solution of 5-chloro-3,3-difluoro-1,3-dihydro-2H-indol-2-one (1.00g, 4.91 mmol) in dry tetrahydrofuran (6 mL) at 0 °C was added borane-tetrahydrofuran complex (13.1 mL, 19.6 mmol, 1.5 M in tetrahydrofuran and diethyl ether) and the reaction mixture was allowed to attain room temperature over 40 h. After careful
20 addition of 2 M aqueous HCl (12 mL) and subsequent neutralization of the reaction mixture with 2 M aqueous NaOH, the mixture was partitioned between dichloromethane and brine. The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were washed with water, dried (Na₂SO₄), and concentrated without heating. Flash column chromatography
25 (hexane/dichloromethane/ 1:1) of the residue gave 437 mg (53 %) of 5-chloro-3-fluoro-1H-indole.

¹H NMR (400 MHz, CDCl₃ as solvent and internal reference) δ 7.00 (t, 1H, *J* = 2.8 Hz), 7.17 (ABdd, 1H, *J* = 1.9, 8.8 Hz), 7.23 (ABdd, 1H, *J* = 2.3, 8.8 Hz), 7.58 - 7.62 (m, 2H).

30

Step C

A vigorously stirred mixture of 5-chloro-3-fluoro-1H-indole (168 mg, 0.991 mmol) in toluene (4 mL) and 2M aqueous NaOH (4 mL) was treated at room

temperature with benzenesulphonyl chloride (190 μ L, 1.49 mmol), and a drop of Aliquat® 336. After 18 h the phases was separated, the aqueous phase was extracted with toluene. The combined organic phases were dried (Na_2SO_4), concentrated and subjected to flash column chromatography (hexane/dichloromethane 2:1) to give 221 mg (72 %) of 5-chloro-3-fluoro-1-(phenylsulphonyl)-1*H*-indole.

^1H NMR (400MHz, CDCl_3 as solvent and internal reference) δ 7.31 - 7.35 (m, 2H), 7.43 - 7.47 (m, 2H), 7.50 (d, 1H, $J = 1.8$ Hz), 7.55 - 7.59 (m, 1H), 7.81 - 7.84 (m, 2H), 7.96 (dd, 1H $J = 1.7, 9.0$ Hz).

10 Step D

n-Butyllithium (0.45 mL, 1.6 M in hexane, 0.72mmol) was added dropwise to a solution of 5-chloro-3-fluoro-1-(phenylsulphonyl)-1*H*-indole (213 mg, 0.688 mmol) in dry THF (2 mL) at -78°C . After 30 min, sulphur dioxide (g) was introduced and condensed in the reaction flask during 10 min and the resulting suspension was then allowed to attain room temperature over 2 h. Hexane was added and the precipitate formed was washed and collected. After repeated cycles of centrifugation followed by decantation of the supernatant, to give 238 mg of the corresponding lithium sulphinate salt. To this salt, suspended in dry dichloromethane (4 mL) at 0°C , was added *N*-chlorosuccinimide (96 mg, 0.72 mmol) and the resulting mixture was stirred for 3 h.

20 The reaction mixture was then filtered through celite and concentrated to give 222 mg of 5-chloro-3-fluoro-1-(phenylsulphonyl)-1*H*-indole-2-sulphonyl chloride which was used in the next step without further purification.

^1H NMR (400 MHz, CDCl_3 as solvent and internal reference) δ 7.46 - 7.51 (m, 2H), 7.61 - 7.69 (m, 3H), 7.94 - 7.97 (m, 2 H), 8.31 (dd, 1H, $J = 1.4, 9.1$ Hz).

25

Step E

A solution of piperazine (62 mg, 0.72 mmol) and triethylamine (0.30 mL, 2.17 mmol) in dry dichloromethane (4 mL) was added to crude 5-chloro-3-fluoro-1-(phenylsulphonyl)-1*H*-indole-2-sulphonyl chloride (295 mg, 0.72 mmol) in dry dichloromethane (2 mL) at 0°C . The reaction mixture was stirred at 0°C for 2h and was then diluted with dichloromethane, washed with saturated aqueous NH_4Cl , dried (Na_2SO_4), and concentrated. Flash column chromatography (dichloromethane/MeOH

30

1:0→20:1) of the residue gave 83 mg of 5-chloro-3-fluoro-1-(phenylsulphonyl)-2-(piperazin-1-ylsulphonyl)-1*H*-indole which was used in the next step without further purification.

¹H NMR (400 MHz, methanol-*d*₄ as solvent and internal reference) δ 2.92 - 2.89 (m, 4H), 3.62 - 3.65 (m, 4H), 7.36 - 7.40 (m, 2H), 7.50 - 7.67 (m, 5 H), 8.18 (d, 1H, *J* = 8.9 Hz).

Step F

To a solution of 4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)benzoic acid (57 mg, 0.25 mmol) in dry *N,N*-dimethylformamide (2 mL) at room temperature was added *N,N*-diisopropylethylamine (86 μ L, 0.49 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (105 mg, 0.33 mmol). After 2 min a solution of crude 5-chloro-3-fluoro-1-(phenylsulphonyl)-2-(piperazin-1-ylsulphonyl)-1*H*-indole (75 mg, ~0.16 mmol) in dry *N,N*-dimethylformamide (2 mL) was added. The reaction mixture was stirred at room temperature for 26h and was then concentrated *in vacuo*. Purification of the residue by reversed-phase preparative HPLC (20→100% acetonitrile in 0.1 M aqueous NH₄OAc) gave 8 mg (9 %) of 6-{4-[4-(5-Chloro-3-fluoro-1*H*-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2*H*-pyridazin-3-one.

¹H NMR (400 MHz, *N,N*-dimethylformamide-*d*₇ as solvent and internal reference) δ 3.20 - 4.10 (m, 8H), 3.79 (s, 3H), 7.04 (d, 1H, *J* = 9.7 Hz), 7.44 (dd, 1 H, *J* = 1.9, 9.0 Hz), 7.58 (d, 1 H, *J* = 8.9 Hz), 7.62 - 7.65 (m, 2H), 8.00 - 8.03 (m, 2H), 8.07 (d, 1H, *J* = 1.8 Hz), 8.12 (d, 1H, *J* = 9.7 Hz).

HRMS (ESI+) calc. [M+H]⁺ 530.1065, found 530.1053.

25 Example 5

6-{4-[4-(5-Chloro-1*H*-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-ethyl-2*H*-pyridazin-3-one

The compound was prepared according to the procedure for Example 1 in 29% isolated yield.

¹H NMR (400 MHz; *N,N*-dimethylformamide-*d*₇ as solvent and internal reference) δ (ppm) 1.36 (t, 3H), 3.16 - 3.28 (m, 4H), 3.50 - 3.90 (m, 4H), 4.22 (q, 2H),

7.04 (d, 1H, $J = 9.9$ Hz), 7.10 (m, 1H), 7.35 - 7.38 (m, 1H), 7.52 (m, 2H), 7.59 (m, 1H), 7.83 (m, 1H), 7.97 (m, 2H), 8.09 (d, 1H, $J = 9.9$ Hz).

HRMS (ESI+) calc. $[M+H]^+$ 526.1316, found. 526.1298

5 **Example 6**

2-Butyl-6-{4-[4-(5-chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one

The compound was prepared according to the procedure for Example 1 in 15% isolated yield.

10 ^1H NMR (400 MHz; *N,N*-dimethylformamide- d_7 as solvent and internal reference) δ (ppm) 0.93 (t, 3H), 1.36 (m, 2H), 1.79 (m, 2H), 3.10 - 3.90 (m, 8H), 4.20 (t, 2H), 7.04 (d, 1H, $J = 9.7$ Hz), 7.10 (m, 1H), 7.35 - 7.38 (m, 1H), 7.52 (m, 2H), 7.59 (m, 1H), 7.83 (m, 1H), 7.97 (m, 2H), 8.09 (d, 1H, $J = 9.7$ Hz).

HRMS (ESI+) calc. $[M+H]^+$ 554.1628, found. 554.1629

15

Example 7

6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-hydroxy-ethyl)-2H-pyridazin-3-one

20 The compound was prepared according to the procedure for Example 10 in 40% isolated yield.

^1H -NMR (400 MHz; dimethyl sulfoxide- d_6 as solvent and internal reference) δ (ppm) 2.90 - 3.85 (m, 8H), 3.77 (t, 2H), 4.20 (t, 2H), 4.82 (m, 1H), 7.02 (m, 1H), 7.04 (d, 1H, $J = 9.7$ Hz), 7.32 (m, 1H), 7.45 - 7.51 (m, 3H), 7.78 (m, 1H), 7.90 (m, 2H), 8.04 (d, 1H, $J = 9.7$ Hz).

25 HRMS (ESI+) calc. $[M+H]^+$ 542.1265, found. 542.1220

Example 8

6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2,2,2-trifluoro-ethyl)-2H-pyridazin-3-one

30 The compound was prepared according to the procedure for Example 1 in 19% isolated yield.

^1H NMR (400 MHz; *N,N*-dimethylformamide- d_7 as solvent and internal reference) δ (ppm) 3.12 - 3.34 (m, 4H), 3.50 - 3.80 (m, 4H), 5.10 (q, 2H), 7.11 (m, 1H),

7.20 (d, 1H, $J = 9.8$ Hz), 7.34 - 7.37 (m, 1H), 7.53 (m, 2H), 7.61 (m, 1H), 7.83 (m, 1H), 7.97 (m, 2H), 8.18 (d, 1H, $J = 9.8$ Hz).

HRMS (ESI+) calc. $[M+H]^+$ 580.1033, found 580.1009.

Example 9

5 6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-methoxy-ethyl)-2H-pyridazin-3-one

The compound was prepared according to the procedure for Example 10 in 35% isolated yield.

$^1\text{H-NMR}$ (400 MHz; dimethyl sulphoxide- d_6 as solvent and internal reference)

10 δ (ppm) 2.96 - 3.26 (m, 4H), 3.25 (s, 3H), 3.30 - 3.80 (m, 4H), 3.75 (t, 2H), 4.31 (t, 2H), 7.03 (m, 1H), 7.05 (d, 1H, $J = 9.7$ Hz), 7.33 (m, 1H), 7.46 - 7.51 (m, 3H), 7.79 (m, 1H), 7.90 (m, 2H), 8.04 (d, 1H, $J = 9.7$ Hz).

HRMS (ESI+) calc. $[M+H]^+$ 556.1422, found. 556.1385

15 Example 10

6-{4-[4-(5-Chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl}-2-[2-(2-methoxy-ethoxy)-ethyl]-2H-pyridazin-3-one

6-[4-({4-[(5-Chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)phenyl]-pyridazin-3-ol (see WO 99/57113, 0.054 gram, 0.11 mmol), 0.016 gram of anhydrous
20 potassium carbonate (0.11 mmol, 1.0 eq.) and 0.02 gram of 1-bromo-2-(2-methoxy-ethoxy)ethane (0.11 mmol, 1.0 eq.) were mixed in 1.5 mL of dry *N,N*-dimethylformamide. The mixture was treated with microwave at 150 °C for 1 hour. Without any work-up, purification was performed on preparative HPLC, which gave 0.023 gram of
25 6-[4-[4-(5-chloro-1H-indole-2-sulphonyl)-piperazine-1-carbonyl]-phenyl]-2-[2-(2-methoxy-ethoxy)-ethyl]-2H-pyridazin-3-one (yield 36 %).

$^1\text{H-NMR}$ (400 MHz; dimethyl sulphoxide- d_6 as solvent and internal reference)

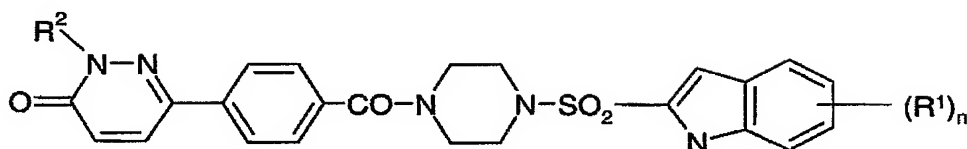
δ (ppm) 2.96 - 3.26 (m, 4H), 3.16 (s, 3H), 3.38 (m, 2H), 3.30 - 3.80 (m, 4H), 3.53 (m, 2H), 3.82 (t, 3H), 4.30 (t, 3H), 7.03 (m, 1H), 7.06 (d, 1H, $J = 9.7$ Hz), 7.33 (m, 1H), 7.45 - 7.51 (m, 3H), 7.79 (m, 1H), 7.91 (m, 2H), 8.04 (d, 1H, $J = 9.7$ Hz).

30 HRMS (ESI+) calc. $[M+H]^+$ 600.1683, found. 600.1671

CLAIMS

1. A compound of formula (I)

5



(I)

wherein R² is amino, a group OR⁴ or a group -Y-R⁵ where

R⁴ is hydrogen or C₁₋₄alkyl,

Y is C₁₋₄alkylene,

- 10 R⁵ is hydrogen, halo, hydroxy, C₁₋₂alkoxy, C₁₋₂alkoxyC₁₋₂alkoxyC₁₋₄, or a group NR⁷R⁸ where R⁷ and R⁸ are independently selected from hydrogen, C₁₋₂alkyl, hydroxyC₁₋₂alkyl or alkoxyC₁₋₂alkyl, or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a saturated 5-6-membered heterocyclic ring which optionally contains an additional heteroatom;
- 15 n is one or two and each R¹ is independently selected from halo, haloC₁₋₂alkyl, hydroxy, oxo, amino, C₁₋₂alkylamino or di-C₁₋₂dialkylamino; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R² is a group -Y-R⁵.

20

3. A compound according to claim 2 wherein Y is a C₁₋₂alkylene group.

4. A compound according to claim 2 or claim 3 wherein R² is methyl.

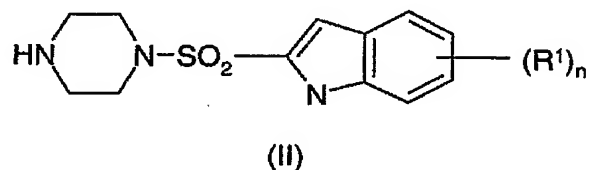
- 25 5. A compound according to claim 1 wherein R² is a group -Y-R⁵ and R⁵ is a group NR⁷R⁸ where R⁷ and R⁸ are independently selected from hydrogen, C₁₋₂alkyl, hydroxyC₁₋₂alkyl or alkoxyC₁₋₂alkyl, or R⁷ and R⁸ together with the nitrogen atom to

which they are attached form a saturated 5-6-membered heterocyclic ring which optionally contains an additional heteroatoms.

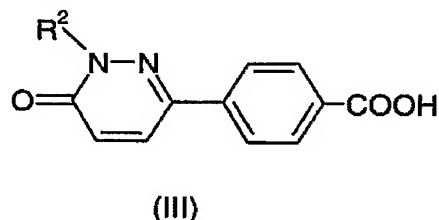
6. A compound according to any one of the preceding claims wherein n is 1.
- 5 7. A compound according to any one of the preceding claims wherein at least one R¹ group is a halo group.
8. A compound according to claim 7 wherein R¹ is bromo or chloro.
- 10 9. A compound according to any one of the preceding claims wherein an R¹ group is present at a position equivalent to the 5-position as numbered on the indole ring.
10. A compound according to claim 1 which is
- 15 1-(5-chloroindol-2-ylsulphonyl)-4-[4-(6-oxo-1-methyl-pyridazin-3-yl)benzoyl]piperazine,
6-[4-({4-[(5-chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)phenyl]-2-[2-(dimethylamino)ethyl]pyridazin-3(2H)-one,
6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-methylamino-ethyl)-2H-pyridazin-3-one,
- 20 6-{4-[4-(5-chloro-3-fluoro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-methyl-2H-pyridazin-3-one,
6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-ethyl-2H-pyridazin-3-one,
- 25 2-butyl-6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2H-pyridazin-3-one,
6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-hydroxy-ethyl)-2H-pyridazin-3-one,
6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-(2,2,2-
- 30 trifluoro-ethyl)-2H-pyridazin-3-one,
6-{4-[4-(5-chloro-1H-indole-2-sulfonyl)-piperazine-1-carbonyl]-phenyl}-2-(2-methoxy-ethyl)-2H-pyridazin-3-one, or

6-[4-((4-[(5-chloro-1H-indol-2-yl)sulphonyl]piperazin-1-yl}carbonyl)phenyl]-2-[2-(2-methoxyethoxy)ethyl]pyridazin-3(2H)-one.

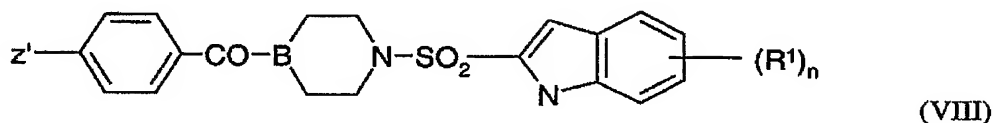
11. A process for preparing a compound of formula (I) as defined in claim 1
 5 which process comprises either
 (a) reacting an amine of formula (II)



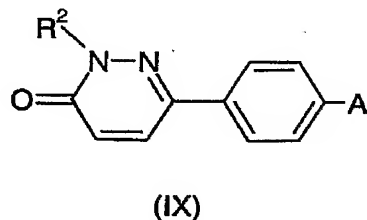
with an acid of the formula (III)



- 10 or a reactive derivative thereof; or
 (b) reacting a compound of the formula (VIII):



- 15 wherein Z' is a displaceable group, with a compound of formula (IX)

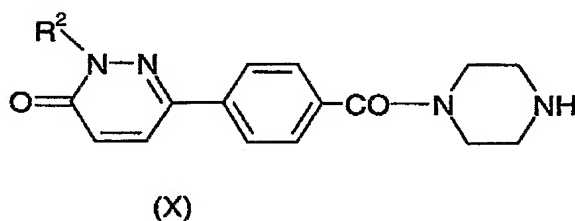


wherein R^2 is as defined claim 1 and A is an activating group, or

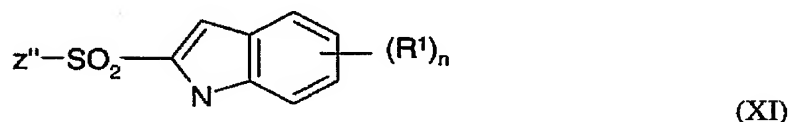
(c) forming a substituted pyridazinone ring on compounds of formula (VIII), wherein Z' is a functional group capable of cyclisation;

(d) by reacting a compound of the formula (X):

5

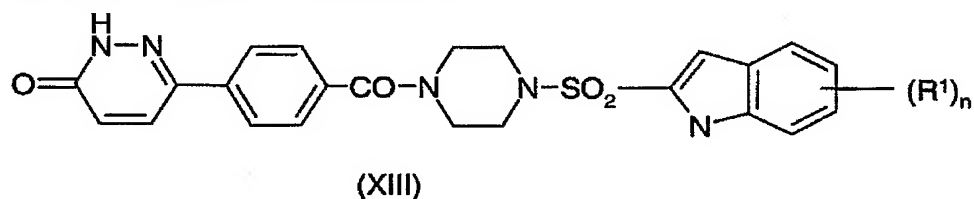


where R^2 is as defined in claim 1, with a compound of the formula (XI):



10 wherein R^1 and n are as defined in claim 1 and Z'' is a displaceable group, under conditions similar to those described above in process (a); or

(e) reacting a compound of formula (XIII)



wherein R^1 and n are as defined claim 1, and the indole ring is optionally protected,

15 with a compound of formula (A)



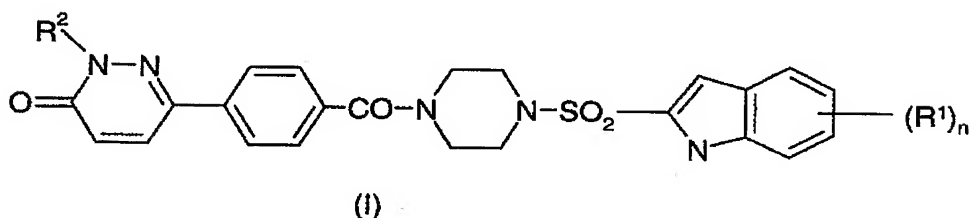
where R^2 is as defined in claim 1 and Z''' is a displaceable group, and thereafter if necessary, removing any indole protecting groups.

12. A compound of formula (I), as defined in any claim from 1 to 8, or a pharmaceutically-acceptable salt thereof for use in medical therapy.
13. A pharmaceutical composition comprising a compound of formula (I), or a
5 pharmaceutically-acceptable salt thereof, as defined in any claim from 1 to 8, with a pharmaceutically-acceptable diluent or carrier.
14. Use of a compound of formula (I), as defined in any claim from 1 to 10, or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in
10 a method of treating a Factor Xa mediated disease or condition.
15. A method of treating a Factor Xa mediated disease or condition in a warm-blooded animal comprising administering an effective amount of a compound of formula (I), as defined in any claim from 1 to 10, or a pharmaceutically-acceptable salt
15 thereof.

Patent Office

A B S T R A C TTITLE : HETEROCYCLIC DERIVATIVES

5 The invention relates to heterocyclic derivatives of formula (I),



- wherein R^2 is amino, a group OR^4 or a group $-Y-R^5$ where R^4 is hydrogen or C_{1-4} alkyl,
- 10 Y is C_{1-4} alkylene, R^5 is hydrogen, halo, hydroxy, C_{1-2} alkoxy, C_{1-2} alkoxy C_{1-2} alkoxy C_{1-4} , or a group NR^7R^8 where R^7 and R^8 are independently selected from hydrogen, C_{1-2} alkyl, hydroxy C_{1-2} alkyl or alkoxy C_{1-2} alkyl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a saturated 5-6-membered heterocyclic ring which optionally contains an additional heteroatom; n is one or two and each R^1 is
- 15 independently selected from halo, halo C_{1-2} alkyl, hydroxy, oxo, amino, C_{1-2} alkylamino or di- C_{1-2} dialkylamino; or a pharmaceutically acceptable salt thereof.

These compounds possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also

20 relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.